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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,958	01/07/2002	Saul Tzipori	21957	5351

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EXAMINER	
NAVARRO, ALBERT MARK	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,958	TZIPORI ET AL.	
	Examiner	Art Unit	
	Mark Navarro	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 26-36 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 26-36 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 9, 2004 has been entered.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. The rejection of claims 26-36 under 35 U.S.C. 103(a) as being unpatentable over Krivan et al and Perera et al in view of Queen et al and Engelman et al is maintained. In view of Applicants amendment, the following new reference is also applied: Williams et al (US Patent Number 6,080,400).

Applicants are asserting that none of the prior art discloses the use of an antibody to only a single subunit of the Stx2 for treatment or prevention of disease. Applicants further assert that none of the prior art recognizes that one only has to block Stx2 to prevent the mortality and other extremely serious complications of HUS

associated with certain highly virulent strains of E. coli. Applicants further assert that there is nothing that would lead one to substitute subunit specific antibodies into the teachings of Krivan, determine an effective dosage, and then have a reasonable expectation of success. Applicants further assert that "Krivan says his antibodies and invention are not, and cannot be, useful in humans."

Applicants arguments have been fully considered but are not found to be fully persuasive.

Applicants arguments are not found to be fully persuasive in view of the combined teachings of Krivan et al, Perera et al, Williams et al, Queen et al and Engelman et al.

First, Applicants are asserting that none of the prior art discloses the use of an antibody to only a single subunit of the Stx2 for treatment or prevention of disease. However, Applicants attention is directed to the teachings of Krivan, which are directed to methods of treatment of SLT toxemia in a human comprising administering a high titer, monospecific antibody against SLT II. It is noted that Krivan et al do not recite which subunit (α or β) the antibodies bind. However, Perera et al teach of five ***neutralizing*** monoclonal antibodies which specifically bound the α subunit of SLT II. (Emphasis added). One of ordinary skill in the art would be motivated to incorporate only antibodies which specifically bind the α subunit of SLT II into the method taught by Krivan in view that the antibodies are reported to be neutralizing.

Second, Applicants further assert that none of the prior art recognizes that one only has to block Stx2 to prevent the mortality and other extremely serious

complications of HUS associated with certain highly virulent strains of E. coli. However, Applicants are again directed to the teachings of Krivan et al. Krivan et al specifically claim methods of "passive immunization" and "treatment" of humans comprising administering an antibody which specifically binds the identical Shiga-like toxin II. (See claims).

Third, Applicants assert that there is nothing that would lead one to substitute subunit specific antibodies into the teachings of Krivan, determine an effective dosage, and then have a reasonable expectation of success. However, as set forth previously, Perera et al teach of monoclonal antibodies to Shiga like toxin II of enterohemorrhagic E. coli which specifically bind the α subunit and are determined to be "neutralizing antibodies." Clearly, one of ordinary skill in the art would appreciate wanting to use a "neutralizing antibody" in a method of treating a toxin in vivo. Furthermore, the teachings of Williams et al (US Patent Number 6,080,400) are also particularly relevant. Williams et al set forth that "Studies of Shiga toxin B subunit suggest that neutralizing epitopes may also be present at both the N- and C-terminal regions of VT1 and VT-2 B subunits. Polyclonal antibodies raised against peptides from these regions (residues 5-18, 13-26, 7-26, 54-67, and 57-67) show partial neutralization of Shiga toxin (I Harari and R. Arnon, Carboxy-terminal peptides from the B subunit of Shiga toxin induce a local and parenteral protective effect, Mol. Immunol. 27: 613-621, 1990; and Harari et al , Synthetic peptides of Shiga toxin B subunit induce antibodies which neutralize its biological activity." Williams et al set forth that VT1 and VT2 correspond to SLT-I and SLT-II, respectively. (See columns 5-7).

Finally, Applicants assert that "Krivan says his antibodies and invention are not, and cannot be, useful in humans." Applicants are again directed to the claims of Krivan et al, which set forth of "A method for the treatment of SLT toxemia in a ***human***" comprising administering the same antibodies that Applicants assert cannot be useful in humans.

The claims are drawn to a dosage formulation comprising an effective amount of humanized monoclonal antibodies, the antibodies consisting of antibodies neutralizing Shiga like toxin II in vivo, wherein the antibodies are specifically reactive with a single subunit of the Shiga like toxin II produced by E. coli which causes hemolytic uremic syndrome, to prevent or treat hemolytic uremic syndrome in a human.

Krivan et al (US Patent Number 5,512,282) teach of purified high titer, monospecific polyclonal antibodies to Shiga-like toxin obtain by a process of inoculating a bovine animal with a purified active SLT derived from E. coli and selected from the group consisting of SLT I, SLT II, SLT IIV and mixtures thereof. Krivan et al further teach of the passive immunization of a human or animal against SLT toxinemia comprising administering to the human or animal a prophylactically effective amount of the elicited antibody. (See Claims 1 and 17). Krivan et al further disclose that SLT toxinemia can lead to hemolytic uremic syndrome. (See column 1). Krivan et al further disclose that "the present invention provides an antitoxin to **one** or more SLTs." (See Column 6). Krivan et al further disclose that "**A single type of SLT, such as SLT-II** or

a variant thereof, such as SLT-IIvp, can be injected. This provides polyclonal antibodies that are monospecific to just that type of SLT or variant." (See column 8).

Perera et al (Journal of Clinical Microbiology Vol. 26, No. 10, pp 2127-2131, October 1988) teach of five monoclonal antibodies which bind to the α-subunit of SLT-II and were able to neutralize the toxin. (See abstract).

Williams et al (US Patent Number 6,080,400) teach of studies of Shiga toxin B subunit suggest that neutralizing epitopes may also be present at both the N- and C-terminal regions of SLT-I and SLT-II B subunits.

None of Krivan et al, Perera et al, or Williams et al teach of monoclonal human or humanized antibodies.

Queen et al (WO 90/07861) teach that methodology for the production of CDR-grafted antibodies having CDRs derived from the variable regions of non-human antibodies and framework regions derived from human antibodies were well established in the art at the time the claimed invention was made and that CDR-grafted antibodies were recognized to be useful reagents for diagnostic and therapeutic applications. Queen et al further set forth that humanized antibodies are substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin. (See abstract).

Engelman et al (Human Hybridomas and Monoclonal Antibodies. New York Plenum Press. 1985 pp 23-27) teach that methods for constructing human-human hybrids that secrete human monoclonal antibodies using lymphoblastoid cell lines as fusion partners were well known in the art at the time of Applicants invention.

Given that 1) Krivan et al have disclosed of methods of passive immunization comprising administering high titer, monospecific polyclonal antibodies against Shiga-like toxin II, and that 2) Perera et al have demonstrated neutralization of SLT-II with monoclonal antibodies which specifically bind the α subunit of SLT-II, and that 3) Williams et al have taught of neutralizing epitopes on the β subunit of SLT-II, and that 4) Queen et al has taught of the advantages of humanized antibodies over non-human antibodies for therapy in humans, and that 5) Engelman et al has also taught of the advantages of human monoclonal antibodies over non-human monoclonal antibodies for therapy in humans, it would have been prima facie obvious to one of ordinary skill in the art to have generated a humanized antibody or a human monoclonal antibody as taught by Queen et al and Engelman et al, for use in the method disclosed by Krivan et al. It would have been further obvious to select antibodies against a single α or β subunit in view of Perera et al and Williams et al demonstration of neutralizing monoclonal antibodies against these specific subunits. One would have been motivated to produce such an antibody based on the advantages described by Queen et al and Engelman et al, (i.e., substantially decreased immunogenicity).

It is noted that the references do not teach the amount of antibodies set forth in claims 34 or 36. However, determining the precise dosage of a humanized antibody is merely the result of optimizing a result effective variable. As set forth in In re Boesch, 617, F.2d 272, 276, 205 USPQ 215, 219, (CCPA 1980), it is normally within the skill in the art to optimize a result effective variable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro whose telephone number is (571) 272-0861. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Navarro
Primary Examiner
April 14, 2004